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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,576	12/05/2003	Praveen Sharma	Q-65721	8084

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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,576	SHARMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/429,003.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/07; 10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/21/07 and 10/29/07 have been entered. The papers have been considered, but are not sufficient to place the application in condition for allowance for the reasons set forth in this office action. A full statement of the rejections is set forth and then a response to applicant's remarks.

2. The interview summary filed 10/29/07 is noted. The interview summary is complete.

3. The declaration filed 9/21/07 has been carefully considered.

4. The declaration establishes that "very early stage breast cancer" is understood to refer to stage 0 breast cancer which includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) (declaration pages 1 and 2). Thus, the recitation in the claims of "very early stage breast cancer" is interpreted as referring to these two types of cancer.

5. The previously set forth rejection for lack of enablement is withdrawn in view of the amendments to the claims and applicant's declaration filed 9/21/07, and also in view of further consideration of the state of the prior art at the time the invention was made, particularly the teachings of Ralph et al. The rejection for lack of written description is maintained. Applicant's

remarks are addressed following a statement of all of the rejections currently pending in this application.

Information Disclosure Statement

6. The information disclosure statement filed 10/29/07 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

7. The paper filed with the IDS indicates that the reference was previously filed in the parent application. However, only the abstract of the reference was previously filed.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 27-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In claim 27 the recitation "specific for said breast cancer" in part (b) of the claim is indefinite because it is not clear if this recitation is referring to the generically recited "breast cancer" in the preamble and part (a) of the claim or "very early stage breast cancer" recited in part (b) of the claim.

11. In claim 28 the recitation "specific for said breast cancer" in part (b) of the claim is indefinite because it is not clear if this recitation is referring to the generically recited "breast

cancer" in the preamble and part (a) of the claim or "very early stage breast cancer" recited in part (b) of the claim.

12. In claim 29 the recitation "specific for said breast cancer" in part (b) of the claim is indefinite because it is not clear if this recitation is referring to the generically recited "breast cancer" in the preamble of the claim or "very early stage breast cancer" recited in part (b) of the claim.

13. Claim 32 refers to "said isolated cDNA" but this is confusing because claims 18 and 19 refer to "isolated cDNA" throughout the method, and it is not clear if this claim requires that any one of these are labeled or if it is intended to require that all of these are labeled. Further, it is noted that this claim is only limiting in the case where the method is performed to produce isolated cDNA, yet all of the claims from which claim 32 depends recite the step of producing isolated cDNA only in the alternative.

14. Claims which are not specifically mentioned are rejected because they depend from those mentioned.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 18 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (US 6,190,857; as cited in IDS) in view of Lukas et al. (Journal of Investigative Medicine, 1997, Vol. 45, No. 1, page 132A).

Ralph et al. teach a method for cancer detection and diagnosis that relies upon detecting a response of circulating leukocytes to the disease state (Col. 4, line 66-Col. 5, line 14). Ralph et al. teach that the method described in their disclosure may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including but not limited to organ defined cancer (Col. 10, lines 2-3). To that end, Ralph et al. teach a method which includes steps of providing human peripheral blood mRNAs from both healthy and diseased individuals, amplifying the mRNAs to provide nucleic acid amplification products, separating the nucleic acid amplification products, and selecting those mRNAs that are differentially expressed between normal individuals and individuals having a disease state (Col. 9, lines 35-43). Ralph et al. further teach a variety of further methods in which the identified markers could be used- to identify and isolate full length gene sequences, cDNA sequences, or to select segments for use in detection, diagnostic or prognostic methods, vector constructs and the like (Col. 16 and throughout). The practice of any of these methods would first require that the differentially expressed markers had been isolated, as required in instant claim 18. Further, when Ralph et al. exemplify their method for the identification of markers of metastatic prostate

cancer, they teach "cutting differentially appearing bands out of the gel" and subsequent cloning and sequencing of the bands (Col. 62, lines 60-65).

The differential display method exemplified by Ralph et al. employs gel electrophoresis as the means to separate the amplification products, and this is a non-sequence based technique (Col. 62, and throughout).

Ralph et al. teach that their method may also comprise the step of converting RNAs into cDNAs using reverse transcriptase (Col. 9 line 45 and following), and they exemplify this step in the methods throughout the document.

Ralph et al. do not teach this method wherein the organ defined cancer is very early stage breast cancer. Ralph et al. do not exemplify a method wherein at least ten differently expressed markers are isolated, nor do they exemplify a method wherein between 50 and 100 are selected or between 10 and 500.

Lukas et al. undertake differential display analysis in order to identify genes which are differentially expressed in breast ductal carcinoma in situ (DCIS) relative to invasive breast carcinoma, and identified 119 mRNA species which were differentially expressed. Lukas et al. teach that the identification and characterization of genes involved in early breast carcinogenesis may further our understanding of the molecular pathogenesis of cancer in general and may also lead to identification of breast-cancer specific molecular markers with potential predictive value.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Ralph et al. so as to have applied them to the study and diagnosis of DCIS, following the guidance of Lukas et al. One would have been motivated by the teachings of Ralph et al. that their methods can be applied to

any organ defined cancer (which DCIS is) and by the teachings of Lukas et al. of the desirably to identify genes involved in early breast carcinogenesis. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have isolated as many differentially expressed markers as possible, including 10, 20, 100, 500, provided that the markers existed in the two sample types. At the time the invention was made, it was widely known that performing differential display methods with different beginning primer sets would result in the isolation of non-redundant sequences, and it was routine to practice the method with a variety of primer sets in order to provide one of skill in the art with the means to gather as many differently expressed markers as possible.

Thus, following the teachings of Ralph et al. in view of Lukas et al., the claimed invention is prima facie obvious.

18. Claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. in view of Lukas et al. as applied to claims above, and further in view of Wadhwa et al. (Molecular Biotechnology, Volume 6, pages 213-217).

The teachings of Ralph et al. in view of Lukas et al. are previously discussed.

Ralph et al. teach that an advantage of their method is that there is no need to directly sample tumor cells in order to detect cancer markers as such markers may instead be detected by sampling circulating cells of the immune system, circumventing the problem of having to first identify the location of a tumor in the body before being able to able to analyze it (Col. 5, lines 45-54). Regarding claims 27, 28, and 29, Ralph et al. teach that once such a disease state marker is identified, various detection methods are known for screening and diagnostic purposes,

teaching, for example that the mRNA species themselves may be detected, for example, by Northern blotting, RT-PCR, slot-blotting, and similar methods well known in the art (Col. 6, lines 43-48). Northern blotting and slot-blotting are both methods include steps of hybridizing test mRNA or cDNA with the marker probes that are cDNA are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have the disease state. Ralph et al. teach that the method of detecting human disease comprises detecting the quantity of a disease marker expressed in human peripheral blood and comparing the quantity of the marker to the quantity expressed in the blood of a normal individual, where a difference in quantity of expression is indicative of a disease state (Col. 10, lines 32-50, and throughout).

However, Ralph et al. in view of Lukas et al. do not teach a method wherein the identified isolated nucleic acid markers are prepared on a solid support, namely a solid support which is a filter.

Wadhwa et al. teach a reverse northern assay of DNA fragments isolated from differential display, and teach that this type of method has advantages over traditional Northern blots, including that it requires less time, and it is particularly useful as many of the isolated bands from differential display are small in size and would not serve a good probes from Northern analysis (p. 216). In this method, the isolated differentially displayed molecules were PCR amplified, bound to a membrane filter, and probed cDNA probes prepared from total RNA from cells. The isolated cDNA probes were labeled.

It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Northern assays taught by Ralph et al. in view of Lukas et al. with the reverse

Northern assays taught by Wadhwa et al. Because both references teach methods for detecting nucleic acids in samples, it would have been obvious to one skilled in the art to substitute one method for the other to achieve the predictable result of detecting target nucleic acids in samples.

19. Claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 27, 28, and 29 each include steps wherein isolated mRNA or isolated cDNA from a sample are hybridized to 10 or more mRNA or cDNA species transcribed from mRNA which are present at a different level in cells in a blood sample from one or more normal humans than in corresponding cells in a blood sample from one or more eukaryotic organisms known to have said breast cancer. The claim further requires that the 10 or more mRNA are "specific" for said breast cancer and that the cells in which they are differentially expressed have not contacted the area of said breast cancer and that the blood sample is obtained from a part of said organism distant to the area of said cancer. Thus, the practice of the claimed method requires the hybridization to a particular set of probes that are identified only by their function (that they are differentially present in two samples and that they are indicative of cancer) and by the type of cell that they were identified within (blood cells that have not touched the area of the disease and that were isolated distant from the area of disease). The specification and claims suggest that there are hundreds of possible genes that meet these requirements (see claim 34, for

example which requires that between 10 and 500 mRNA species are used). The scope of the claim is thus quite broad with regard to the actual sequences used. There are tens of thousands of possible genes within the human genome.

The application does not provide any descriptive support of even a single example of an appropriate mRNA or cDNA probe for use in the claimed methods. The specification generally suggests that such probes could be identified for cancer, but does not describe a single sequence that falls within the scope of the requirements for sequences in step (b) of the rejected independent claims. Thus, there is no actual reduction to practice. There is no detailed drawing or chemical formula or even gene name to suggest molecules that would be useful in the claimed invention. There is no disclosure of sufficient, relevant, identifying characteristics of the molecules essential to practice the claimed invention, other than a general disclosure of their function. The specifically generally suggests such molecules as are necessary to practice the claimed invention might exist, but the specification does not provide any written description as to what the structure of these molecules is. Thus, the claims are rejected for lack of adequate written description.

Double Patenting

20. Claims 18-~~38~~ 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-36 of copending Application No. 11/149370. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claims in the copending application require steps that are generic to the instantly claimed invention since the independent claims in the copending application encompass methods relative to any disease. These claims do have very similar steps

to those in the instant invention, namely they specifically recite blood cells that are obtained from a part of said human distant to the area of disease and have not contacted said area of said disease. Likewise, each of the limitations of the dependent claims in the instant application are provided in dependent claims in the copending application. Claims 35 and 36 recite embodiments wherein said disease is "cancer" and wherein said disease is "stomach, lung, breast, prostate, and bowel cancer." Thus, given all of these recitations, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have practiced the methods set forth in the copending application and applied those methods to cancer, and more particularly any or all of the cancer types recited in the claims of the copending application, including breast cancer. One would have been motivated to practice such an invention by the express presence of these embodiments as claimed embodiments.

21. Applicant has previously argued on this record that very early breast cancer is a situation wherein the "blood has not contacted said area of disease." Thus in order to have practiced the method claimed in the copending application as it is written for the study of breast cancer, the method would have necessarily resulted in the practice of the instantly claimed method. Therefore, the rejection is maintained for the instantly pending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

On page 11 of the paper filed 9/21/07 applicant states that Ralph et al. relates to the detection of metastatic cancers, and thus in no way relates to the instantly claimed invention.

However, this is not persuasive because, while Ralph et al. does discuss metastatic breast cancer, Ralph et al. also clearly and directly teaches that their method can also be applied to organ defined cancers. Ralph et al. are very clear that it is changes in blood cells that are being measured, and that these changes are a response to the presence of disease, as cited in the rejection and discussed throughout Ralph et al.

Applicant's remarks concerning enablement are moot in view of the withdrawal of the enablement rejection in this office action.

On page 15 of the paper filed 9/21/07 applicant states that "the invention does not lie in the particular probes that are isolated, but rather in the samples which are used." However, in claims 27-35 this is not accurate- the invention requires both. The practice of the claimed method requires the probes which are recited in the claims.

Applicant states on pages 16 the paper filed 9/21/07 that "The sequence of the probes is not of importance. The relevant issue is instead whether suitable probes can be obtained." Applicants suggest that with regard to written description they merely need to communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. The examiner disagrees. The court has made it clear that with regard to chemical compounds, the standard for written description is possession, not enablement or intent to claim. "While we have no doubt a person so motivated would be enabled by the specification to make it, this is beside the point for the question is not whether he would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. We think it does not." In Re Ruschig, 379 F.2d 990, 995, 154 U.S.P.Q. 118, 123 (CCPA 1967). Furthermore, the court stated "Accordingly, naming a type of material generally

known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." The Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q.2d 1406 (Federal Circuit 1997). In the instant case, although applicant have provided a general functional description of the probes necessary for practicing the claimed invention (i.e. their differential expression and specificity for breast cancer), this is not sufficient to convey possession of the entire possible group of any set of 10 or more probes that meet this requirement as are required for the practice of the instant claims. The fact that these molecules are differentially expressed in humans having very early breast cancer relative to humans who do not have very early stage breast cancer is not sufficient to provide the specific sequences which are essential for their use as probes or for the use of any hybridizing portion of these genes as primers and probes.

The rejection for lack of written description is maintained.

The double patenting rejection is maintained. No arguments were presented to traverse the rejection.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

January 31, 2008